Journal of Surgical Oncology 1997;66:196–200

Intraoperative Intrapleural Hypotonic Cisplatin Treatment for Carcinomatous Pleuritis

YUKITO ICHINOSE, MD,* TOKUJIRO YANO, MD, HIROSHI ASOH, MD, HIDEKI YOKOYAMA, MD, YASURO FUKUYAMA, MD, JUN MIYAGI, MD, SHINJI KUNINAKA, MD, AND YASUHIRO TERAZAKI, MD

Department of Chest Surgery, National Kyushu Cancer Center, Fukuoka, Japan

Background and Objectives: We recently developed a new intraoperative intrapleural hypotonic cisplatin treatment for carcinomatous pleuritis found at thoracotomy in non-small cell lung cancer patients. In the present study, the efficacy and adverse events of this treatment as well as the pharmacokinetics of cisplatin in the blood after the treatment were evaluated.

Patients and Methods: Twenty-one patients received the treatment for 15 minutes after completing the intrathoracic surgical procedures. The total and free platinum levels in the blood of five patients were then measured. As a control, 29 patients without such treatment were reviewed retrospectively.

Results: The survival rates in the treatment and non-treatment groups were similar. The pleural disease free survival of the treated patients was, however, significantly higher than that of the non-treated patients. Such pleural disease as effusion and the growth of the pleural disseminated tumors only appeared in three of the 21 (14%) treated patients while 26 of 29 (90%) non-treated patients had clinically detected pleural disease. The blood platinum levels after the treatment were extremely low and such low levels probably induced no systemic adverse events after the treatment. The only adverse event of this treatment was an increase in the postoperative drainage volume.

Conclusions: These observations seem to suggest that intraoperative intrapleural hypotonic cisplatin treatment for carcinomatous pleuritis found at thoracotomy can, at least, delay the appearance of the pleural disease without any adverse events.

J. Surg. Oncol. 1997;66:196–200.

KEY WORDS: **non-small cell lung cancer; carcinomatous pleuritis; malignant effusion; cisplatin; intracavitary chemotherapy**

INTRODUCTION

We sometimes encounter patients whose carcinomatous pleuritis including carcinomatous effusion and/or pleural dissemination is not identified by preoperative examinations. Since a surgical resection is thought to be contraindicated in such patients, the open thorax is generally closed without any treatment. In our prior retrospective study, however, we found that the survival of such patients found at thoracotomy in whom the primary tumor was resected was significantly prolonged compared to those whose operation resulted in no resection [1].

Contract grant sponsor: Ministry of Health and Welfare, Japan; Contract grant number: 8S-1.

*Correspondence to: Dr. Yukito Ichinose, Department of Chest Surgery, National Kyushu Cancer Center, 3-1-1, Notame, Minami-ku, Fukuoka 815, Japan. Fax: 81-92-551-3083; E-mail: yichinos@nk-cc.go.jp

Accepted 4 August 1997

Regardless of resecting or not resecting the primary tumor, sooner or later these pleural lesions produce such symptomatic problems as dyspnea due to massive pleural effusion and chest pain associated with the growth of pleural disseminated tumors. Therefore, an important issue in maintaining the patient's quality of life is to control the advance of pleural disease for as long as possible. To potentially solve this problem, we developed an intraoperative intrapleural treatment regimen in which distilled water was combined with cisplatin [2]. In the present study, we retrospectively compared the survival and control of pleural disease in 21 patients who had received intraoperative intrapleural hypotonic cisplatin treatment with the findings of 29 patients who had not been administered such treatment. The adverse effects of the treatment as well as the pharmacokinetics of cisplatin in the blood after treatment were also examined.

PATIENTS AND METHODS

Patients

The carcinomatous pleuritis of non-small cell lung cancer was found at thoracotomy in 29 patients from 1972 to 1988 and in 21 patients from 1988 to 1996 at the National Kyushu Cancer Center. Neither carcinomatous pleural effusion nor pleural disseminated tumors were diagnosed preoperatively. The latter 21 patients also underwent an intraoperative intrapleural hypotonic cisplatin treatment. In 13 (45%) of the former 29 patients, anticancer drugs such as Adriamycin and mitomycin C or microbial pleurodesis agents such as cell wall skeleton of Bacillus Calmette-Guérin and dried streptococci (OK432) were administered to the thoracic cavity either intraoperatively or postoperatively. In this study, the patients with carcinomatous pleuritis found at thoracotomy were classified into two groups depending on whether or not they had received intraoperative intrapleural hypotonic cisplatin treatment. The patient characteristics of these two groups are shown in Table I. Postoperative radiotherapy for unresected tumors was performed on three patients from the treatment group and on seven patients from the non-treatment group. Systemic cisplatin-based chemotherapy after operation was administered to three patients from the treatment group and to one patient from the non-treatment group. To analyze the adverse events of the hypotonic cisplatin treatment, another 17 patients, the majority of whom had pleural disease detected by intraoperative pleural lavage cytology, were also included. To comparatively evaluate the amount of postoperative drainage volume, 60 patients without carcinomatous pleuritis, who underwent a lobectomy from 1988 to 1996, were randomly selected and also included in our analysis

TABLE I. Characteristics of Patients With Carcinomatous Pleuritis Found at Thoracotomy

	No treatment (n = 29)	Hypotonic cisplatin treatment (n = 21)	*P* value
Age: mean ± S.D.[a]	60 ± 9	59 ± 12	0.92
(range)	(44–78)	(32–77)	
Male/female	14/15	13/8	0.34
Histology			
Adenocarcinoma	20 (70%)	17 (81%)	0.34
Others	9 (30%)	4 (19%)	
N factor			
N0–1	14 (48%)	8 (38%)	
N2	13 (45%)	11 (52%)	0.76
Nx	2 (7%)	2 (10%)	
Disseminated nodules			
(+)	29 (100%)	19 (90%)	0.09
(−)	0	2 (10%)	
Carcinomatous effusion			
(+)	12 (41%)	16 (76%)	0.01
Little or unknown	17 (59%)	5 (23%)	
Operation (primary tumor)			
No resection	15 (52%)	2 (10%)	
Wedge resection	—	6 (29%)	
Lobectomy	14 (48%)	6 (29%)	0.00
Pneumonectomy	—	7 (33%)	

[a]S.D., standard deviation.

Intraoperative Intrapleural Hypotonic Cisplatin Treatment

The actual procedure of this treatment was as follows: After completing the intrathoracic surgical procedures, the thoracic cavity was washed out with saline to remove any blood and then was washed out an additional two more times with distilled water. Thereafter, the entire thoracic cavity was exposed for 15 minutes to cisplatin in distilled water that was prewarmed to from 38°C to 40°C. The cisplatin concentration used was 50 μg/ml. After sucking the solution and washing out the thoracic cavity with saline, two chest tubes were inserted and then the thoracic cavity was closed. Perioperative hydration was not performed. This treatment was approved by the institutional review board, and informed consent was obtained from all patients.

Measurement of Blood Cisplatin Levels

Blood samples of five patients who underwent a lobectomy and intraoperative intrapleural hypotonic cisplatin treatment (administered cisplatin dose: 100 mg) were collected at 1, 2, 6, 12, 24 and 48 hours following the start of intraoperative intrapleural cisplatin treatment. The serum was obtained by centrifugation at 1,000 rpm for 10 minutes in order to measure the concentrations of total platinum (free platinum plus protein bound platinum). A part of the serum was then transferred into an Amicon Centrifree MPS-3 tube (Amicon, Inc., Beverly, MA) and centrifuged at 3,000 rpm for 60 minutes at 4°C

in order to collect the filtered serum which was used to measure the free platinum levels. The cisplatin-derived platinum was determined by flameless atomic absorption spectrophotometry [3]. The threshold of measurement in total and free platinum was 50 ng/ml and 25 ng/ml, respectively. The pharmacokinetic parameters were estimated using standard methodology [4]. The area under the concentration (AUC) time curve was estimated by the trapezoidal approximation. Whenever feasible, a linear regression was used to estimate drug half-lives (t½s).

Follow-Up

All the patients were followed-up and the follow-up examination was, in general, done every 2 months for the first 2 years and thereafter every 3 to 4 months unless any symptoms appeared, and included a physical examination, complete blood count, blood chemistry, and chest radiography. Appearance of pleural disease after the operation was defined as the time when fluid accumulation and/or pleural thickness or pleural nodular shadow were radiologically detected. The radiological changes in all the patients who developed pleural disease were confirmed to be progressive.

Statistical Analysis

The overall survival and pleural disease free survival rates were calculated from the operation day using the method of Kaplan and Meier, and a statistical comparison of these findings was performed using the two-tailed log-rank test. In the analysis of the pleural disease free survival, patients who died without the appearance of pleural disease were censored at the date of death. Any differences between the proportions were evaluated using either the chi-square test or Student's *t*-test. The statistical difference was thus considered to be significant when the *P* value did not exceed 0.05.

RESULTS

As of February 1997, of the 21 patients in the hypotonic cisplatin treatment group, six were still alive with a survival ranging from 10 to 53 months (a median of 41 months) after the operation while one patient died of cardiovascular disease and the other 14 died due to cancer spread. In the non-treatment group, all 29 patients died of cancer. As shown in Figure 1, no significant difference was found in the survival between the two groups.

However, the control of pleural disease in the hypotonic cisplatin treatment group was significantly better than that in the non-treatment group (Fig. 2). In the non-treatment group, 26 (90%) patients demonstrated pleural effusion and/or the growth of pleural disseminated tumors from 1 to 34 months (a median of 9 months) after the operation. When a duplication was allowed, 14 patients had pleural effusion and 16 patients showed a growth of the pleural disseminated tumors. Of 14 patients with pleural effusion, five patients underwent closed chest tube drainage due to dyspnea induced by massive pleural effusion. Of the latter 16 patients, 11 patients suffered from chest pain due to the growth of the disseminated tumors. On the other hand, in the hypotonic cisplatin treatment group, pleural disease was only observed in three (14%) patients after the operation. Two demonstrated disseminated tumor growth and one had pleural effusion.

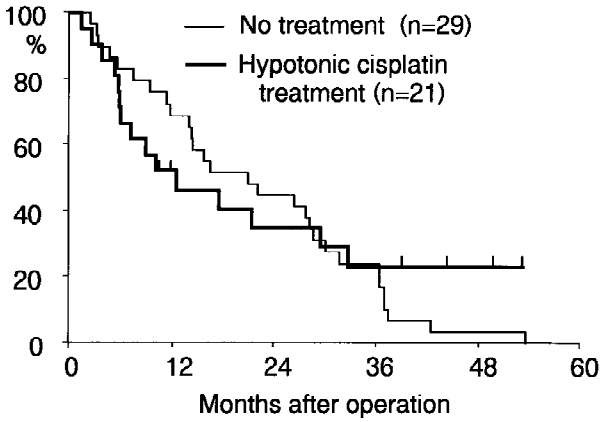

Fig. 1. Survival of patients with carcinomatous pleuritis treated with/without hypotonic cisplatin treatment. The ticks indicate patients who are still alive. $P = 0.69$ by the log-rank test.

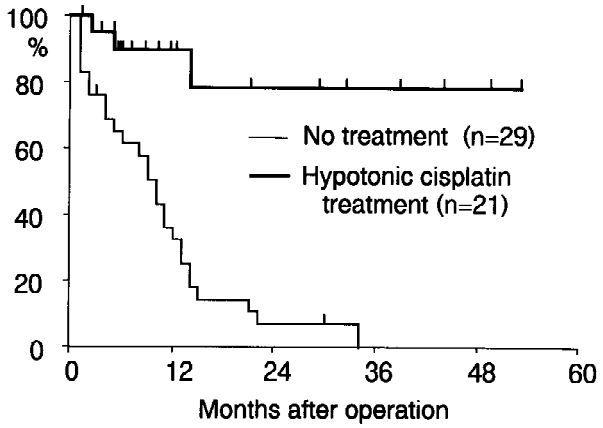

Fig. 2. Pleural disease free survival of patients with carcinomatous pleuritis treated with/without hypotonic cisplatin treatment. The ticks indicate patients who are either alive or dead but who did not demonstrate any occurrence of pleural disease. $P < 0.0001$ by the log-rank test.

In 11 of the 21 patients who underwent the hypotonic cisplatin treatment, postoperative drainage fluid was examined for the presence of cancer cells. One patient had some degenerated cancer cells while the other 10 patients had no cancer cells in the drainage fluid after the operation.

As shown in Table II, the postoperative drainage volume roughly correlated with the extent of the resection.

TABLE II. Postoperative Drainage Volume and the Period of Drainage in 38 Patients Receiving Hypotonic Cisplatin Treatment

Operative procedure	Drainage volume (ml)		Period of drainage (days)	
	Range	Mean ± S.D.[b]	Range	Mean ± S.D.
No resection (n = 3)	300–1743	881 ± 761	2–6	3.3 ± 2.3
Wedge resection or segmentectomy (n = 6)	340–1510	836 ± 419	2–7	4.3 ± 2.2
Lobectomy (n = 22)	240–8130	2244 ± 1780*	3–13	6.3 ± 2.5*
Pneumonectomy (n = 7)	190–1780	1085 ± 509	1–4	2.6 ± 1.1
Lobectomy[a] (n = 60)	355–2920	1095 ± 550	2–11	4.2 ± 1.5

[a]Patients who did not receive hypotonic cisplatin treatment.
[b]S.D., standard deviation.
*$P < 0.0001$, as compared to a lobectomy without hypotonic cisplatin treatment, as calculated by Student's *t* test.

When compared to patients with a lobectomy who did not receive the hypotonic cisplatin treatment, the postoperative drainage volume in the patients with a lobectomy receiving the hypotonic cisplatin treatment was significantly higher and the period of drainage was also significantly longer. Except for this problem, however, all patients recovered uneventfully after the operation. In addition, no bone marrow suppression, abnormal renal function, or intestinal symptoms that were related to the administration of cisplatin were observed.

Figure 3 shows the changes in the total and free platinum levels in the serum following the start of the hypotonic cisplatin treatment. The mean total platinum level which was 263 ng/ml at 1 hour after treatment decreased with time and reached 87 ng/ml at 48 hours. The mean AUC for total platinum was 5.5 ± 2.3 μg/ml/hour ranging from 3.3 to 9.2. The t½ for total platinum was 29.2 ± 13.7 hours ranging from 15.1 to 49.6. On the other hand, serum free platinum rapidly decreased. The mean free platinum level was 79.5 ng/ml at 1 hour and thereafter reached an undetectable level at 2 hours.

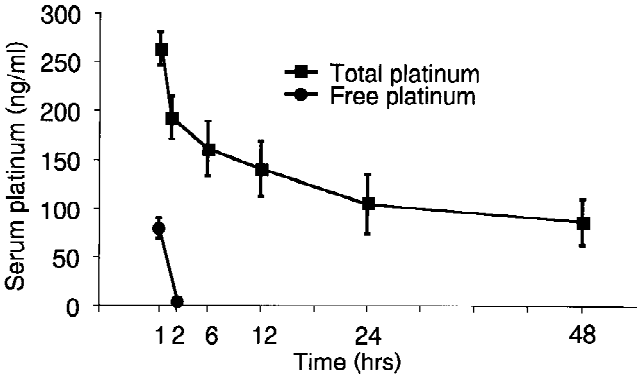

Fig. 3. Concentration of the total and free platinum in the blood of the patients following intraoperative intrapleural hypotonic cisplatin treatment. The mean ± standard deviation of platinum level is shown.

DISCUSSION

For the treatment of patients with clinically detected carcinomatous pleuritis, especially malignant pleural effusion, an intrapleural administration of sclerosing agents such as talc is commonly used. In fact, thoracoscopic talc insufflation or instillation of talc slurry through a chest tube has been reported to successfully control malignant pleural effusion in more than 90% of patients treated [5,6]. The mechanism of the control of pleural effusion by talc treatment is due to the effect of pleurodesis which obliterates the pleural space and thus prevents a reaccumulation of the effusion. Therefore, it has nothing to do with eradicating cancer cells and disseminated tumors present in the pleural space. Intracavitary cisplatin-based chemotherapy, which is cytotoxic rather than sclerosing, has proven to be safe and effective via the intraperitoneal route in ovarian cancer [7,8]. However, the management of malignant pleural effusion using intrapleural cisplatin-based chemotherapy seems to be more difficult as compared to that using a sclerosing agent. According to the review of Walker-Renard et al. [5], the success rate of that treatment in the control of pleural effusion was only 27% while systemic adverse effects were observed frequently.

The main difference between the previously reported intrapleural cisplatin-based chemotherapy and our intraoperative intrapleural hypotonic cisplatin treatment is the use of isotonic saline in the former and distilled water in the latter for a dilution of cisplatin which itself is an isotonic solution [2,9]. The mechanism by which the hypotonic cisplatin treatment shows an anti-tumor effect is considered to be as follows: 1) distilled water itself has a direct cytotoxicity [2], 2) tumor cells exposed to hypotonic cisplatin increase their cellular cisplatin level since the cells become swollen by the hypotonic solution [2]

and 3) such species as chloro-aqua and diaqua, which are formed by the hydrolysis of cisplatin in distilled water, are also believed to be active anti-tumor agents [10,11]. Thus, the intraoperative intrapleural hypotonic cisplatin treatment using cisplatin and distilled water is thought to have a synergistic anti-tumor effect which might result in a high local control rate and the disappearance of cancer cells in drainage fluid after the operation in patients with carcinomatous pleuritis found at thoracotomy.

Another difference between the above mentioned treatments is treatment time. Rusch et al. [12] reported that the absorption of the intrapleurally administered drug into the blood circulation was rapid with peak blood levels being reached within 1 hour of the instillation. In a previous report on intrapleural chemotherapy, at least 4 hour exposure of the pleural space to anti-cancer drugs was performed [9]. Therefore, 76% and 52% of all patients who received intrapleural cisplatin-based chemotherapy experienced gastrointestinal adverse events (nausea/vomiting) and bone marrow suppression, respectively [5]. In our treatment, the exposure time of the pleural space to the hypotonic cisplatin was only 15 minutes. The mean concentration of serum total platinum at 1 hour was 263 ng/ml in the present study while that at 1 hour after intrapleural instillation with the same dose of cisplatin as ours was reported to be as high as 2,000 ng/ml [13]. The free platinum level which is toxic [11] was also low and reached an undetectable level in the blood at 2 hours. With respect to the AUC for total platinum in the blood, the AUC reported by Rusch et al. [12], who used intrapleural administration of 100 mg/m^2 cisplatin, was more than ten times higher than that in the present study. These pharmacokinetic data of platinum in the blood thus support our observations that there were no systemic adverse effects in our treatment. The only adverse effect was the increase in the postoperative drainage volume. This was thought to be due to the destructive change of the mesothelial layer after exposure to hypotonic cisplatin [2]. However, this damage was temporary because the intrapleural fluid was gradually absorbed over time after removal of the chest tube.

In conclusion, the intraoperative intrapleural cisplatin treatment seems to have an anti-tumor effect on the carcinomatous pleuritis which was found at thoracotomy in patients with non-small cell lung cancer. Although no definitive conclusions can be drawn from this retrospective study, the present observations suggest that the above described treatment can, at least, delay the appearance of the pleural disease without any adverse effects.

ACKNOWLEDGMENTS

We thank Mr. Brian Quinn for his critical review, and Ms. Yumiko Oshima for her help in the preparation of the manuscript.

REFERENCES

1. Ichinose Y, Hara N, Ohta M, Yano T, Maeda K, Hata K: Survival of patients with non-small cell lung cancer undergoing incomplete resection or exploratory thoracotomy with no resection. Lung Cancer 1993;8:265–274.
2. Ichinose Y, Hara N, Ohta M, et al.: Hypotonic cisplatin treatment for carcinomatous pleuritis found at thoracotomy in patients with lung cancer. J Thorac Cardiovasc Surg 1993;105:1041–1046.
3. LeRoy AF, Wehling ML, Sponseller HL, et al.: Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. Biochem Med 1977;18:184–191.
4. Gibaldi M, Perrier D (eds): ''Pharmacokinetics.'' 2nd ed. New York: Dekker, 1982.
5. Walker-Renard PB, Vaughan LM, Sahn SA: Chemical pleurodesis for malignant pleural effusions. Ann Intern Med 1994;120:56–64.
6. Yim APC, Chan ATC, Lee TW, Baker TR, Emrich LJ, Hartman AB: Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. Ann Thorac Surg 1996;62: 1655–1658.
7. Piver MS, Lele SB, Marchetti DL, Wan IYP, Ho JKS: Surgically documented response to intraperitoneal cisplatin, cytarabine, and bleomycin after intravenous cisplatin-based chemotherapy in advanced ovarian adenocarcinoma. J Clin Oncol 1988;6:1679–1684.
8. Reichman B, Markman M, Hakes T, et al.: Intraperitoneal cisplatin and etoposide in the treatment of refractory/recurrent ovarian carcinoma. J Clin Oncol 1989;7:1327–1332.
9. Rusch VW, Figlin R, Godwin D, Piantadosi S: Intrapleural cisplatin and cytarabine in the management of malignant pleural effusions: A lung cancer study group trial. J Clin Oncol 1991;9: 313–319.
10. Rosenberg B: Platinum complex-DNA interactions and anticancer activity. Biochimie 1978;60:859–867.
11. Sherman SE, Lippard SJ: Structural aspects of platinum anticancer drug interactions with DNA. Chem Rev 1987;87:1153–1181.
12. Rusch VW, Niedzwiecki D, Tao Y, et al.: Intrapleural cisplatin and mitomycin for malignant mesothelioma following pleuroectomy: Pharmacokinetic studies. J Clin Oncol 1992;10:1001–1006.
13. Yasumoto K, Shimokawa T, Nagashima A, Hirose N, Nakahashi H: Pharmacokinetics of cisplatin instilled into the pleural cavity following panpleuropneumonectomy in patients with malignant pleurisy due to lung cancer. J Surg Oncol 1993;54:67–70.